Specialty Conference

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This is a transcript of one of the regular teaching conferences in Infectious Diseases held weekly at Harbor General Hospital, Torrance, California. These conferences have been edited by Doctors Jerrold A. Turner, John Z. Montgomerie, Anthony W. Chow, Thomas T. Yoshikawa and Lucien B. Guze.

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Infectious Disease Emergencies

PART I:
Patients Presenting with an Altered State of Consciousness

PHYLLIS OILL, MD:* This is the first part of a five part symposium concerned with medical emergencies related to infectious diseases. The format of this symposium is based on the major symptom complex that a patient may exhibit when presenting to an emergency department or physician's office. At the beginning of each section of the symposium there is a chart of the various infectious diseases that may be etiologically responsible for the patient's clinical symptomatology (see Table I-1). Only those entities most commonly associated with the clinical situation being considered in the particular part of the symposium will be discussed. The other listed infectious processes will be covered in those sections in which the clinical factors related to that disease entity are most dominant. For example, although infective endocarditis may manifest in a patient as an altered state of consciousness it will be discussed in the section dealing with patients who present with cardiac decompensation (Part II).

The first part of the symposium will consider those infectious diseases that may primarily cause an altered state of consciousness in a patient. Patients presenting to the emergency department with alterations of their sensorium (such as lethargy, stupor or coma) pose a difficult diagnostic and therapeutic problem to a physician. The urgency and complexity of this clinical state are due to several factors:

- Rapid irreversible brain damage may occur unless decisive therapeutic interventions are quickly employed;
- Key and important medical history is often unobtainable;
- The differential diagnoses are numerous, and
- Rapid mobilization and assistance from various medical and surgical specialties (such as neurologist, neurosurgeon, neuroradiologist, cardiologist and infectious disease specialist) may be necessary in the total management of the patient.

It is beyond the scope of this symposium to systematically discuss all the possible causes of lethargy, stupor and coma, or how to differentiate each clinical entity. However, a list of the more common disease states that may present as alterations of the sensorium is shown in Table I-2. The list is by no means complete but it should provide physicians with a practical differential diagnosis when faced with a patient with this clinical problem.

The first discussant is Dr. Thomas Yoshikawa, who will address himself to the topic of suppura-

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Part I of a five part symposium. Parts II through V will be published in subsequent issues.

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ABBREVIATIONS USED IN TEXT

CNS = central nervous system
CSF = cerebrospinal fluid
HSV = herpes simplex virus
KOH = potassium hydroxide
LP = lumbar puncture
PMN = polymorphonuclear

tive intracranial processes: meningitis, brain abscess, subdural empyema and cerebral phycomycosis. Dr. Terry Yamauchi will then discuss viral meningitis and encephalitis. In addition, he will consider Reye's syndrome, which often follows a viral-like illness although an etiologic agent has yet to be determined.

THOMAS T. YOSHIKAWA, MD:* In keeping with the purpose of this symposium, the discussion will be directed toward diagnosis and management of intracranial infections that may present in the patient as lethargy, stupor or coma. Helpful clues which may assist the physician in suspecting an intracranial infectious process are listed in Table I-3. Although none of these findings will specifically rule in or rule out an intracranial infection, they may heighten the suspicion of the physician toward this diagnosis. Failure to make a rapid diagnosis and begin appropriate therapy is the major reason for the morbidity and mortality seen in patients with intracranial infections.

Meningitis

Meningitis, especially those types with bacterial causes, epitomizes the major impact antimicrobial agents have made in the modern practice of medicine. Before the antimicrobial era, bacterial meningitis was a disease with a *mortality* exceeding 90 percent. However, with early diagnosis and institution of appropriate antimicrobial therapy, the *cure* rate can approach 90 percent. Therefore, it is imperative that the physician—whether it be in an emergency room, clinic or office—who first sees a patient exhibiting lethargy, stupor, coma or even more subtle central nervous system (CNS) signs be keenly attuned to this possible diagnosis.

Clinical Features

Some of the helpful clinical findings in suspecting meningitis are listed in Table I-3. The usual rapidity in which the symptoms and signs appear in patients with meningitis, in association with fever, makes it absolutely essential that physicians think *first* of meningitis—until it can be proved not to be present. However, in nonbacterial meningitis (tuberculous or fungal) the clinical features may be more gradual and indolent. More subtle clinical findings may be the predominant feature, such as a change in personality, mild confusion and low-grade fever. A history of tuberculosis, abnormal findings on an x-ray film of the chest, appropriate travel history, underlying malignancies or use of immunosuppressive drugs may be helpful clues to direct physicians in considering meningitis in these less overt presentations.

Diagnosis

Once the possibility of meningitis is suspected, examination of the cerebrospinal fluid (CSF) is the *sine qua non* in confirming this diagnosis. A lumbar puncture (LP) should then be carried out. However, before an LP is done, the physician should consider whether a *localized* intracranial suppurative process (for example, brain abscess or subdural empyema) may be a strong consideration in the differential diagnosis. (The clinical features of these two disease entities will be subsequently discussed.) If this is the case, a brain scan or arteriogram, or both, should be done *before* initiating a lumbar puncture to confirm or exclude these possibilities. Whereas a lumbar puncture is essential for the diagnosis of meningitis, it is potentially hazardous in the presence of a localized intracranial suppurative (or mass) process.[1] Because of the significant risks of herniation syndromes, the hazards of an LP with the latter disease entities far outweigh the useful information that can be obtained from examination of the CSF. In situations where meningitis is associated with intracranial hypertension, or both a meningeal inflammatory process and localized intracranial suppuration (for instance, brain abscess rupturing into the subarachnoid space) are operative, a cisterna magna puncture would be an alternative diagnostic approach for obtaining CSF.

Once a lumbar puncture is carried out, CSF manometric, protein and glucose determinations; cell count with differential; appropriate cultures, and Gram stain should be done. A useful approach in assisting physicians in suspecting a bacterial versus nonbacterial meningitis is to sep-

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arate the CSF white cell count into predominately polymorphonuclear (PMN) response or predominately lymphocytic response. Listed in Table I-4 are the various diagnostic possibilities of an abnormal CSF pleocytosis. A preponderance of PMN's (arbitrarily defined here as 90 percent or greater) is most often associated with untreated bacterial meningitis. However, early in viral (aseptic), tuberculous or fungal meningitis it is possible to see a major PMN response in the CSF. The clinical course, rapid reversion of the CSF to primarily lymphocytes, absence of bacteria on smear or culture and relatively normal spinal fluid glucose levels will strongly suggest a viral cause. The numerous causes of CSF lymphocytosis make it imperative that physicians systematically approach the various diagnostic possibilities, keeping foremost in mind those CNS diseases that are treatable (for instance, tuberculosis, fungal infection, brain abscess, subdural empyema).

The importance of a Gram stain in every case of suspected meningitis cannot be overemphasized. A Gram stain will give positive results 75 percent of the time in patients with culture-proven bacterial meningitis.[2] It is inexpensive, simple, rapid and oftentimes diagnostic. However, the absence of visible bacteria on smear does not exclude the possibility of bacterial meningitis and, therefore, results of the CSF culture become very important. Although the yield may be low, acid-fast smear and India ink preparation should be routinely carried out on CSF.

Cerebrospinal fluid cultures for bacteria, fungi, mycobacteria and virus should be obtained in all patients suspected of having meningitis. The most common bacterial causes of meningitis are pneumococci, Hemophilus influenzae and meningococci.[2-4] Because the latter organism is fastidious, it is important to emphasize that the CSF should be directly inoculated onto a chocolate agar plate at the *bedside*. Additionally, the yield in recovery of meningococci on chocolate agar may be increased if the plate is warmed at least to 25°C before inoculation, since the organism grows best at 35 to 37°C.[5] It should be remembered that if patients have received antibiotics previously, the CSF culture may be negative despite the clinical features and other CSF measurements suggesting a bacterial meningitis.[6,7]

The CSF glucose level is most often depressed (hypoglycorrhachia) in bacterial causes of meningitis but less so with viral causes. Exceptions to this are mumps meningoencephalitis[8] and occasionally herpes meningitis.[9] In tuberculous and fungal meningitis there can also be low values for CSF glucose.[10,11] Normally, the glucose in the CSF will be approximately 60 percent of the blood glucose value;[12] values less than this are usually abnormal.

The spinal fluid protein level is generally elevated to a greater degree in bacterial (and tuberculous or fungal) meningitis compared with that in viral meningitis. However, because of the tremendous overlap that often occurs, this measurement has limited value in assessing possible causes of meningitis.

Other diagnostic studies that are extremely helpful are blood cultures and fungal serology. The former yields positive findings in at least 50 percent of patients with bacterial meningitis.[2] The latter test, in addition to fungal culture, is most useful in diagnosing coccidioidal and cryptococcal meningitis. With coccidioidal CNS involvement, any titer in the CSF complement fixation test is significant.[13] Furthermore, a rising complement fixation titer in the serum, especially

TABLE I-1.—*Infectious Diseases Presenting as Altered States of Consciousness*

Intracranial infections
Meningitis
Subdural empyema
Brain abscess
Cerebral phycomycosis (mucormycosis)
Encephalitis
Viral meningoencephalitis
Reye's syndrome
Infective endocarditis*
Septic shock*
Retropharyngeal abscess with CNS extension†
Necrotizing pneumonia with respiratory insufficiency†

*Discussed in Infectious Disease Emergencies, Part II: Patients Presenting with Cardiac Decompensation and Circulatory Insufficiency (Shock).

†Discussed in Infectious Disease Emergencies, Part III: Patients Presenting with Respiratory Distress Syndromes.

TABLE I-2.—*Differential Diagnosis of Lethargy, Stupor and Coma*

Cranial trauma
Cardiovascular
Hypoperfusion (sepsis, cardiogenic, hypovolemic, etc.)
Cerebrovascular (bleed, thrombosis, emboli)
Metabolic (hypoxemia, electrolyte imbalance, hypoglycemia, hyperglycemia, acidosis, uremia, hepatic failure, hypothyroidism, etc.)
Drugs and toxins (heroin, sedative-hypnotics, alcohol, bromides, arsenic, etc.)
Noninfectious intracranial mass lesions (primary tumor, metastatic lesions)
Intracranial infections (brain abscess, subdural empyema, meningitis, encephalitis, phycomycosis)

above 1 to 32, suggests disseminated disease. Cryptococcal serology is best utilized by measuring for cryptococcal antigen and antibody,[14,15] both in the CSF and serum.

Treatment

Therapy of bacterial meningitis is fairly straightforward based on knowledge of the most common pathogens isolated in this disease. In the adult population, pneumococci and meningococci are the most common CSF isolates. Penicillin G given intravenously in large doses (20 million units per day) is the drug of choice for these two organisms. Ampicillin may also be used with almost equal efficacy. If patients are allergic to penicillin, chloramphenicol (4 grams per day) given intravenously is the alternative agent of choice. The cephalosporins should be avoided because of their relative ineffectiveness in the treatment of bacterial meningitis.[16] In an immunosuppressed person or patients with malignancy, unusual pathogens such as Listeria or Gram-negative bacilli are more commonly isolated.[17] In the absence of a definitive identification of an organism, the initial choice of antimicrobial therapy in these patients with presumed bacterial meningitis will have to be effective against these pathogens. With Gram-negative bacillary meningitis, parenteral gentamicin alone may not suffice and intrathecal supplementation often is necessary.[18] An accepted regimen would be gentamicin given intravenously at a dose of 5 mg per kg of body weight per day with intrathecal gentamicin administered every 18 to 24 hours in a dosage of 4 to 8 mg.[19]

In the pediatric age group, H. influenzae, meningococci and pneumonococci are the major bacteria recovered from the CSF. Therefore, ampicillin given initially, until specific identification of the organism can be made, is the drug of choice. The recommended dosage for ampicillin is 200 to 300 mg per kg of body weight per day. Chloramphenicol can be substituted in penicillin-allergic patients. Also, in areas where there is a high incidence of ampicillin-resistant H. influenzae, both ampicillin and chloramphenicol may be instituted until sensitivity data return. Then one or the other antibiotic can be discontinued, based on this information. In neonatal bacterial meningitis, Gram-negative bacillary organisms are frequently isolated and, therefore, appropriate therapy for these pathogens must be provided.[20]

With partially-treated meningitis (patients receiving prior antibiotics), appropriate cultures still should be obtained. Initiation of antibiotic therapy will be a clinical judgment depending on toxicity of the patient, clinical history and abnormalities found in the various CSF measurements. If antimicrobial agents are withheld, it is imperative that the patient be carefully observed and the CSF reexamined in 12 to 24 hours. Delayed response or unexpected deterioration should prompt the physician to begin antibiotic therapy. Either penicillin G or ampicillin would be the agent of choice.

Tuberculous meningitis should be treated with a minimum of two drugs, preferably isoniazid and

TABLE I-3.—*Clinical Findings Helpful in Suspecting Intracranial Infections*

Exclude other causes by history, physical examination and laboratory data
History or presence of:
- upper and/or lower respiratory infection;
- pericranial infection (ear, mastoid, sinuses);
- penetrating head injuries, craniotomy;
- fever, nuchal rigidity, focal neurological signs;
- evidence of peripheral infections—i.e. endocarditis, lung abscess, empyema;
- heart disease with right-to-left shunt

Abnormal lumbar puncture
Avoid lumbar puncture in suspected brain abscess or subdural empyema
Think of diagnosis

TABLE I-4.—*Differential Diagnosis of Cerebrospinal Fluid Pleocytosis*

Predominantly Polymorphonuclear cells (PMN) (>90 percent)
- Bacterial meningitis
- Early viral meningitis
- Early tuberculous or fungal meningitis
- Occasionally brain abscess or subdural empyema
- Chemical arachnoiditis

Predominantly Lymphocytes (<90 percent PMN's)
- Viral meningitis or encephalitis (ECHO, Coxsackie, mumps, herpes)
- Tuberculous or fungal meningitis
- Partially-treated bacterial meningitis
- Central nervous system syphilis
- Brain abscess or subdural empyema
- Leptospirosis
- Listeria (variable)
- Cysticercosis (Taenia solium)
- Naegleria meningoencephalitis (variable)
- Central nervous system collagen vascular disease
- Central nervous system tumor
- Cerebrovascular accident
- Subdural hematoma
- Multiple sclerosis
- Central nervous system sarcoidosis
- Guillain-Barré
- Etc.

ethambutol. Whether addition of a third agent such as streptomycin is advantageous is unclear. With proven tuberculous meningitis, use of corticosteroids may have some value, especially in the face of cerebral edema or spinal block.[10] In patients with suspected but not documented tuberculous meningitis, use of corticosteroids should be avoided since the possibility of fungal meningitis must still be excluded. Steroids may enhance disseminated fungal disease.

Fungal meningitis can only be effectively treated with parenteral amphotericin B. Coccidioidal meningitis requires not only intravenous but also intrathecal administration of amphotericin B. Therapy is prolonged, often requiring up to a total of 5 grams of this drug for clinical and bacteriologic cures. Cryptococcal meningitis may not require intrathecal administration of amphotericin B, depending on severity of the disease and clinical status of the patient. The role of 5-fluorocytosine in the treatment of fungal infections has yet to be clearly defined, although preliminary data appear somewhat promising.[21,22]

The usual viral (aseptic) meningitis is caused by the enteroviruses, mainly Coxsackie and ECHO. Treatment is mainly supportive since the disease is usually self-limited. Dr. Yamauchi will further elaborate on this topic.

Brain Abscess

The topic of brain abscess has been recently reviewed in a symposium published previously in the WESTERN JOURNAL.[1] For a detailed discussion of this disease entity, the reader should refer to that article. However, a few major points are worth reemphasizing.

Although antibiotics have made a major impact on the mortality of most infections including bacterial meningitis, the death rate in cases of brain abscess has not improved in the past 20 years. A mortality rate of approximately 40 percent has been fairly constant. Those reports of higher survival rates most likely reflect earlier diagnosis and therapy.[23]

Earlier diagnosis depends on increased clinical suspicion by physicians. Although brain abscess is an infectious process, its clinical presentation may not be one of a classical infection (fever, chills, leukocytosis and so forth). Rather its initial mode of presentation may mimic other noninfectious intracranial processes.

A useful approach to classifying the types of clinical presentation in cases of brain abscess has been recently discussed.[1] Briefly, this approach categorizes brain abscess into four basic clinical syndromes, which are listed below.

- Type I—*Rapid Focal Mass Expansion*

Patients appear with symptoms and signs of a rapidly progressive, localized intracranial mass lesion. Neurological progression may be rapid, usually in days to weeks but occasionally within hours. The initial differential diagnosis often includes spontaneous intracerebral hematomas, metastatic neoplastic tumors and malignant astrocytomas.

- Type II—*Intracranial Hypertension*

With this syndrome, the clinical presentation is one of predominantly neurological deterioration secondary to intracranial hypertension. Complaints of nausea, vomiting, headache and alteration of mental function and personality are commonly seen. Papilledema is a common finding. Focal neurological deficits may also be present but are not the major component of this syndrome.

- Type III—*Diffuse Destruction*

Signs and symptoms of a rapid progressive, destructive brain process characterize this syndrome. In these patients there is neurological deterioration out of proportion to estimated intracranial pressure. Papilledema is generally not present with deterioration occurring in the absence of brain herniation. Usually patients with multiple cerebral emboli present in this manner.

- Type IV—*Focal Neurologic Deficit*

Clinical features of focal neurologic deficits evolving slowly is the major finding in this type of brain abscess presentation. A meningioma or slowly growing, benign glioma is often the initial diagnosis.

Knowledge of the various predisposing factors for the development of brain abscess will often assist in heightening the suspicion for this infection. *Pericranial infection* (ear, mastoid or sinus) is a common source of infection preceding the development of brain abscess. *Hematogenous* or *metastatic* spread of infection from a distant focus is not uncommonly encountered as a cause of abscesses of the brain. Pulmonary infections (such as empyema, abscess or bronchiectasis), peripheral osteomyelitis, intraabdominal infec-

tions and infective endocarditis are frequent sources. Brain abscesses secondary to endocarditis tend to be multiple and are associated with high mortality. *Congenital heart disease* with right-to-left shunt is also a frequent predisposing factor to brain abscess. The associated cerebral intravascular thrombosis and right-to-left shunt, allowing bacteremia to bypass the lung, are probable important pathogenic mechanisms. *Cranial trauma* or *surgical operation* may lead to brain abscess formation either by direct implantation of microorganisms into cerebral tissue or by extension of secondary infected scalp, bone flap or cranial osteomyelitis.

The microbial flora of brain abscess is predominantly aerobic and anaerobic streptococci and coagulase-positive staphylococci. Aerobic Gram-negative bacilli are also encountered but with a lesser incidence. Mixed infections of several organisms including anaerobes and aerobes are not uncommon.[23] Familiarity with the microbial flora of the various infected predisposing sites, which result in subsequent development of brain abscess, will often assist in anticipating the types of pathogens that may be encountered with this infection. For example, pericranial infections are often caused by anaerobic and aerobic streptococci; cranial injuries are commonly secondarily infected with coagulase-positive staphylococci and occasionally aerobic Gram-negative bacilli. Additionally, patients' underlying disease may play a significant role in kinds of pathogens isolated in brain abscess—for example, in cancer patients almost half of the organisms recovered from cerebral abscesses are Gram-negative bacilli.[17]

Therapy of brain abscess is two-fold: institution of antimicrobial agents with concurrent surgical evacuation of the abscess. Use of antibiotics alone will not suffice. This was adequately shown in a recent report of six cases of brain abscess which failed to respond to antibiotic therapy alone, despite therapeutic concentrations of the agents in the abscess fluid.[24] Also implied in this study was that initiating antimicrobial therapy did not alter the yield of bacteriological data. If proper culture techniques including anaerobic methods are used, isolation of pathogens in a significant number of instances should be anticipated.

The choice of initial antibiotic therapy should be determined on the basis of the Gram stain results on the abscess fluid. By and large this therapy will generally be use of penicillin since most of the pathogens isolated from brain abscess reported in the literature are sensitive to this agent. However, if staphylococci, Gram-negative bacilli or Bacteroides are seen on smear, appropriate antimicrobial agents for these organisms should be selected. Ultimate chemotherapeutic management will rest on culture identification of the pathogens.

Once the diagnosis of brain abscess is strongly considered, surgical evacuation must be contemplated. If any delay in a drainage procedure is anticipated, intravenous administration of penicillin G, 20 million units a day in divided doses, should be instituted before surgical operation. In penicillin-allergic patients, chloramphenicol, 4 to 6 grams a day given intravenously, would be an alternate choice. Initiation of antimicrobial therapy as soon as possible is important because (1) the associated cerebritis can only be effectively managed with chemotherapeutic agents and (2) prevention of potential bacteremia and contamination of surrounding cerebral tissue during operation may be minimized. From the previous study mentioned,[24] it would not be anticipated that the yield of cultural data should diminish with institution of immediate antibiotic therapy. Systemic antibiotic therapy should be maintained for at least 2 to 3 weeks after surgical drainage. Longer duration of treatment may be necessary depending on the extent of disease and clinical response.

The choice of surgical drainage technique is beyond the scope of this symposium, and details of this can be found elsewhere.[1] However, it should be emphasized that *early surgical intervention* and *adequate drainage* are key factors in the patients' ultimate prognosis.

Subdural Empyema

Subdural empyema is another central nervous system infection classified under localized intracranial suppurative process. It is often discussed together with brain abscess because of the similarity in clinical presentation, microbiological flora and therapeutic management. Therefore, a lengthy discussion will not be presented on this clinical entity.

A few salient features of this disease, however, should be emphasized. The infection is a collection of purulent material in the subdural space and is essentially an abscess. The most common predisposing factor to the development of subdural empyema is an associated sinusitis, most

commonly frontal sinus involvement. In a patient presenting with rapidly developing, focal neurological symptoms and signs with an associated sinus infection, this diagnosis should strongly be considered. Often such patients initially may be thought to have bacterial meningitis. However, helpful clues in differentiating these two entities are (1) the presence of focal neurological signs in subdural empyema which is less common in adults with bacterial meningitis (unless the patient is severely ill); (2) the cerebrospinal fluid in subdural empyema may be "benign" (there may be only mild changes in cells, protein and glucose) as compared with that in bacterial meningitis.

The microbial flora of subdural empyema has been recently reviewed.[25] Streptococci and staphylococci have been most frequently isolated in the past. However, with more sophisticated anaerobic techniques, the role of anaerobic bacteria in subdural empyema appears to be increasingly important. Again, as in brain abscess, the so-called "sterile" subdural empyema may be related to the failure to adequately isolate anaerobes.

The management of subdural empyema is similar to that of brain abscess. Use of antibiotics in concert with surgical drainage are the key elements for a successful therapeutic outcome. The approach to antimicrobial therapy should be the same as in patients with brain abscess. Moreover, because of the similarity in microbial flora in both subdural empyema and cerebral abscess, the choice of antibiotics will not be dissimilar.

Cerebral Phycomycosis

Cerebral phycomycosis is caused by aerobic, saprophytic fungi belonging to the class Phycomycetes. The three species of organisms in this class most commonly associated with disease in man are the genera Mucor, Rhizopus and Absidia.[26] The organisms appear as broad, nonseptated branching hyphae which are ubiquitous in decaying vegetation, fruits, soil and manure. They may be found normally in human orifices (nose, throat and rectum) and are generally noninvasive. However, under certain disease conditions the organism can become highly virulent with invasion into blood vessel walls and subsequent thrombosis and tissue necrosis.[27] Diabetes mellitus with ketoacidosis is most frequently associated with cerebral (rhinocerebral) phycomycosis. Additionally, other predisposing factors include burns, uremia, diarrheal diseases, immunosuppressive states, prior antibiotic therapy and blood dyscrasias. Besides eye and central nervous system involvement, phycomycosis has been reported to occur in other sites such as maxilla,[27] ear[28] and lung,[29] or may disseminate to any organ or tissue in the body.[27]

The pathogenesis in cerebral phycomycosis is initially the development of local lesions in the oral cavity and subsequently direct extension and intravascular spread into adjacent paranasal sinuses, cribiform plate and orbital structures. The infection then may extend to the meninges and cerebral structures.

Clinically, the symptoms and signs may be nonspecific, reflecting the local involvement. However, with full-blown cerebral phycomycosis the classic triad of (1) unilateral proptosis with cellulitis, (2) ophthalmoplegia with blindness and (3) paranasal sinusitis[30] in a diabetic patient with ketoacidosis should alert a physician to this diagnosis. Other clinical manifestations include blood-tinged nasal discharge, black necrotic turbinates, progressive lethargy despite adequate therapeutic management of diabetes, unilateral headache and focal neurological signs.[26]

The differential diagnosis includes bacterial sinusitis, cavernous sinus thrombosis, Wegener's granulomatosis, malignancy, bacterial CNS infection and aspergillosis. To make a diagnosis of phycomycosis, tissue involved with the disease must be cultured for the fungi. Histopathology of tissue with appropriate staining may also confirm this diagnosis. If oral or nasal mucosa appear to be invaded, scrapings from these areas prepared with potassium hydroxide (KOH) may show the broad nonseptated hyphae under light microscopy. Showing the presence of these characteristic hyphae in the appropriate clinical setting will make a presumptive diagnosis of phycomycosis. Serological tests for these organisms are not available and examination of the CSF will not be useful in establishing the presence of cerebral phycomycosis.

Treatment of cerebral phycomycosis is directed toward (1) control of diabetes mellitus or underlying disease, (2) local excision of the involved tissue and (3) institution of parenteral amphotericin B. The minimal cumulative dose of amphotericin B recommended has been 3 grams with renal toxicity being the limiting factor.[26] Despite these measures, the overall mortality has been exceedingly high. Only prompt recognition with early therapy and possibly the development

of more effective chemotherapeutic agents will cause the survival rate to improve in patients with this disease entity.

Viral Meningitis

TERRY YAMAUCHI, MD:* In 1925, Wallgren[31] characterized a syndrome of aseptic or benign meningitis. His criteria for the diagnosis of this entity include (1) the acute onset of illness with signs and symptoms of meningeal irritation, (2) pleocytosis, (3) absence of bacteria in cerebrospinal fluid, (4) a short clinical course without complication, (5) absence of any signs of parameningeal disease or systemic infection that might have meningitis as a complication and (6) absence in the community of epidemic disease that might be associated with meningitis. The clinical features of this syndrome are fever, headache, nuchal rigidity and lymphocytic pleocytosis.

Although there are a large number of viral agents capable of infecting the central nervous system, for the sake of brevity I will only discuss the most common agents associated with this syndrome. Of the viruses implicated, enterovirus and mumps virus account for 90 percent of the proven cases of aseptic meningitis.[32,33]

A seasonal variation is seen in aseptic meningitis caused by these agents. Most enterovirus-associated diseases occur during the warmer months of the year with peak months in Southern California being July, August and September. Mumps virus-associated central nervous system disease is more common during the winter and spring months.[34]

The signs and symptoms of viral meningitis may vary considerably from patient to patient. Fortunately, most of these illnesses are benign and self-limited. The first symptom is often headache of acute onset, usually described as retroorbital or frontal in nature. In children this is not always a major complaint, while in adults the pain may be severe enough to require sedation and analgesics. In contrast to headaches, fever may be notably elevated in children and only mild to moderately increased in adults. With some of the enterovirus infections, a diphasic or triphasic fever pattern has been described.[35] Concurrent with fever, a variety of other symptoms may occur. These include sore throat, lethargy, myalgias, nausea, vomiting, generalized malaise and nuchal rigidity.

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When meningeal irritation is suspected, the following physical signs must be sought: (1) *Nuchal rigidity*, the patient is unable to place the chin on chest, (2) *Kernig's sign,* pain occurs in the hamstring area with efforts to extend the flexed knee beyond 90 degrees and (3) *Brudzinski sign,* when one extended leg is passively flexed, a similar involuntary movement occurs in the other leg.

Other less commonly encountered symptoms of viral meningitis are photophobia, tinnitus, dizziness, chest and abdominal pain, paresthesia and convulsions.

The duration and intensity of these signs and symptoms are extremely variable. In most cases recovery begins within a week of the illness and is complete within the next several days to several weeks. In general, the younger the stricken person is, the shorter the recovery period is and the less severe the symptoms are. Recently, at the Western Society for Pediatric Research Meetings in Carmel, California, a group of investigators from Seattle presented some provocative data on the long-term follow-up of a number of children with enteroviral infections of the central nervous system.[36] The findings of this study suggested that children infected with enterovirus during the first year of life had significantly lower IQ's, smaller head circumferences and language impairments.

When considering the differential diagnosis of viral meningitis one must first contemplate other entities that may be potentially life-threatening disease processes and require vigorous, specific therapy. Bacterial meningitis must be ruled out as early as possible. The indiscriminate use of antibiotics has on many occasions made the diagnosis of viral versus bacterial meningitis difficult. There are several excellent review articles that well summarize this controversial problem.[6,7,37] When confronted with this dilemma, a physician has two choices: either treat the patient as having bacterial meningitis and administer intravenous antibiotics for 10 to 14 consecutive days or carefully monitor the patient for 12 to 24 hours off antibiotics and repeat a lumbar puncture.

Other infectious agents must also be considered in the differential diagnosis of viral meningitis. Tuberculous meningitis is often initially misdiagnosed as having a viral cause. In addition, mycoses such as Cryptococcus or Coccidioides, rickettsiae, protozoae and parasites must be ruled out before making a diagnosis of viral meningitis. Other systemic disease processes such as leuke-

mia, Hodgkin's disease, infectious mononucleosis, catscratch fever, pemphigus and benign infectious lymphocytosis can also mimic meningitis. Heavy metal poisoning, drug ingestion and head trauma are rare causes of meningitis symptomatology.

Laboratory findings play an important role in establishing the diagnosis of viral meningitis. In children, the peripheral leukocyte count may be variable, but a pronounced elevation of the leukocyte count with a polymorphonuclear response is usually seen in bacterial infections. Serological diagnosis depends upon a change in antibody titer when comparing acute and convalescent sera and therefore is not helpful early in the course of illness. However, certain diseases such as syphilis can be eliminated from consideration early with serological studies. Immediate examination of cerebrospinal fluid must be carried out in every case of suspected meningitis. Although the CSF in viral meningitis is usually clear in appearance, on occasion it is opalescent and may have greater than a 1,000 leukocytes per ml. The more usual range is 15 to 500 cells. The predominant cell type is mononuclear but early in the course of illness a polymorphonuclear cell response occurs. Other measures shown to be useful in the CSF of patients with viral meningitis include protein content (usually elevated but may be normal) and glucose content (usually normal and occasionally low). Hypoglycorrhachia has been reported in meningitis associated with both mumps and herpes simplex viruses.[8,9]

CSF samples should be cultured for viral agents as well as bacteria. In our viral diagnostic laboratory a presumptive diagnosis of enterovirus has been possible within 48 to 72 hours after lumbar puncture. Viral cultures from the nasopharynx and stools are also helpful in establishing a viral agent.

At present there is no proven effective specific therapy available for viral meningitis. The therapeutic use of deoxyribonucleic acid (DNA) inhibitors such as adenine arabinoside and cytosine arabinoside has been advocated in some severe viral infections, but the efficacy remains largely unproved.[38-40] Similarly, interferon inducers have been used experimentally for modifying viral infections.[41,42] More information is necessary before this type of therapy can become universal. Fortunately, viral meningitis is largely a self-limited disease and only symptomatic treatment is necessary. Analgesic-antipyrexic agents, maintaining adequate fluid and caloric intake are the basis of symptomatic therapy. More severe cases may require control of seizures, reduction of cerebral edema or increased intracranial pressure, and management of coma.

In addition to the general discussion of viral meningitis, some mention of herpes simplex virus (HSV) infection of the central nervous system should be noted. HSV infections have been recognized as an important cause of CNS disease in humans. Clinically HSV meningitis may be indistinguishable from meningitis due to other viral agents.[43] HVS infection of the CNS accounts for up to 19 percent of all cases of encephalitis[44] and often has extremely variable clinical features.[45] Generally, fever and headache are common early in the disease, but because the HSV can cause focal necrosis, early localized signs may also be present.[46] A patient with HSV encephalitis may present with drowsiness, confusion, disorientation, hallucinations and bizarre behavior. Although a wide variety of seizures may be seen, a common presenting feature is major motor seizures, often unilateral. Dysphagia and aphasia are frequently noted early in the disease. Sensory deficits such as paresthesias may precede the more severe CNS signs. Evidence of meningeal irritation may be present.

The lumbar puncture findings can also be extremely variable, from completely normal results to evidence of a pleocytosis, erythrocytes and elevated protein content. As mentioned earlier, low CSF glucose levels have been documented with HSV infections.[9] The pleocytosis is often a mixture of lymphocytes and polymorphonuclear cells, but may consist of lymphocytes only.[44]

Further diagnostic evaluation includes an electroencephalogram, brain scan and cerebral angiography. If findings on these tests make the diagnosis of HSV encephalitis probable, then a brain biopsy is recommended. Treatment for this disease with systemic antiviral agents or interferon inducers is now under investigation.

Reye's Syndrome

In 1963, Reye and co-workers described a syndrome of acute onset of encephalopathy with hepatic involvement and no other apparent clinical cause of the cerebral and hepatic abnormalities.[47]

Reye's syndrome is primarily an illness of children. Cases have been reported from a few months of age through adolescence.[48] In most of

these cases there occurred a prodrome of fever and upper respiratory symptoms followed by sudden, rapid central nervous system dysfunction and vomiting. Vomiting is such a consistent and early finding that at one time it was considered a necessary feature to clinically diagnose this syndrome. Delirium may present early in the course of illness and often progresses to coma. Seizures, as a manifestation of central nervous system dysfunction, occur in approximately 85 percent of clinically diagnosed cases. In many children mild hepatosplenomegaly and irregular respirations will develop. Often a rash is evident and represents an antecedent illness or precipitating factor. Varicella has been the exanthem most frequently described and this virus has been postulated as a causative agent in Reye's syndrome.[49,50]

Laboratory findings play a major role in diagnosing and guiding therapy in a child with this disease process. Liver involvement is characteristic, and serum levels of glutamic oxalacetic transaminase, glutamic pyruvic transaminase and blood ammonia are commonly elevated. Hypoglycemia is also a usual laboratory abnormality and the glucose concentration in the cerebrospinal fluid parallels the decreased values in the blood. Increased intracranial pressure has been another frequent finding, and some physicians have suggested monitoring and control of this as a valuable adjunct to treatment.[51]

Several viruses have been implicated in the cause of this unusual illness. Viruses which have been associated with this syndrome include Herpesvirus hominis, hepatitis, Coxsackie A, ECHO, adenovirus, reovirus, influenza viruses A and B, rubella, rubeola, parainfluenza and varicella.[52-57] For a virus alone to manifest infection in the human host as described, that agent would need to cause cerebral damage, and also produce a cellular toxin that interferes with intracellular metabolism leading to an accumulation of fat within the viscera.[58] Chang and co-workers[59] have reported a cytopathic agent they call "lipovirus," which produces a toxin capable of inducing fatty degeneration within cultured human cells.

For the present, the strongest link between a viral agent and Reye's syndrome involves the influenza viruses. Epidemiological studies have clearly shown an increase in Reye's syndrome associated with temporal and geographic areas within the United States and influenza B outbreaks.[53,60,61] Norman and co-workers isolated influenza B from the liver of a patient both antemortem and postmortem.[62] In a number of children stricken with this disease and in other family members there have been shown to be notably elevated titers of hemagglutination-inhibiting antibody to influenza B virus.[60] Influenza B infection within the community was documented concurrently by culture or serological techniques, or both.

The mortality ranges between 50 and 100 percent with this syndrome and most conventional forms of therapy have failed to influence the outcome.[47,63-65] More recently, encouraging results have been reported from various institutions in patients treated by hemodialysis, peritoneal dialysis, insulin and glucose infusion, and exchange transfusions.[66-68] In this hospital during the past eight months we have seen remarkable improvement in two children following repeated exchange transfusions. Further studies into the cause and pathogenesis of this disease process are needed. Currently a collaborative program to evaluate various therapeutic approaches is in progress and may aid us in treating this devastating disease in the future.

TRADE AND GENERIC NAMES OF DRUGS

Penicillin G	*penicillin G*
Polycillin®, Omnipen®, Totacillin®, Amcil®, Penbritin®, Principen®	*ampicillin*
Chloromycetin®	*chloramphenicol*
Fungizone®	*amphotericin B*
Ancobon®	*5-fluorocytosine*
INH®, Triniod®, Nydazid®	*isoniazid*
Myambutol®	*ethambutol*
Streptomycin	*streptomycin*
Cytarabine®	*cytosine arabinoside*
Adenosine arabinoside	*adenosine arabinoside*
Garamycin®	*gentamicin*

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